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QT Interval Shortening After Bariatric Surgery Depends on the Applied Heart Rate Correction Equation

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Abstract

Background A shortening of electrocardiographic QT interval has been observed in obese subjects after weight loss, but previous results may have been biased by inappropriate heart rate (HR) correction.

Methods Electrocardiography (ECG) recordings of 49 (35 females) severely obese patients before and 12 months after Roux-en-Y gastric bypass (RYGB) surgery were analysed. QT interval (QTc) was calculated by using four different equations, i.e. *Bazett*, *Fridericia*, *Framingham* and *Hodges*.

Results Irrespectively of the used correction formula, QTc interval length was reduced after the surgery (QTc_{Bazett} −31 ± 18 ms; $QTc_{Fridericia}$ −12 ± 15 ms; $QTc_{Framingham}$ −14 ± 15 ms; QTc_{Hodges} −9 ± 15 ms; all *P*s < 0.001), but QTc_{Bazett} reduction was significantly greater than the reduction in QTc calculated upon the other three equations (all *P*s < 0.001). Moreover, changes in QTc_{Bazett} ($P < 0.001$) but not in $QTc_{Fridericia}$, $QTc_{Framingham}$ and QTc_{Hodges} (all *P*s > 0.05) were significantly correlated with concurrent changes in HR. Multivariate regression analyses revealed a significant independent association of serum insulin levels with $QTc_{Fridericia}$, $QTc_{Framingham}$ and QTc_{Hodges} values (all *P*s < 0.05) preoperatively, whilst changes in QTc interval length after the surgery were not consistently associated to concurrent changes in metabolic traits.

Conclusions Our data show that the extent of weight loss-associated QTc interval shortening largely depends on the applied HR correction equation and appears to be overestimated when the most popular Bazett's equation is used.

Keywords Prolonged QTc · Cardiac hyperpolarization · Morbid obesity · Roux-en Y gastric bypass · Bazett's formula

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Introduction

Obesity is associated with an increased risk for cardiovascular diseases and premature death [1, 2]. An abnormal ventricular repolarization, which predisposes to sudden death upon cardiac arrhythmia [3], may contribute to the increased mortality risk since obesity has been found to be associated with a high prevalence of a prolonged QT interval in electrocardiographic (ECG) recordings [4]. Furthermore, weight loss, in particular when induced by bariatric surgery, has been found to reduce QT interval (QTc) length in many studies (for overview see Table 1) [5–22]. However, the validity of this observation has been challenged by one previous study [9] that demonstrated that the significance of QTc shortening upon weight loss gets lost when the QT interval is corrected for heart rate (HR) by using Fridericia or Framingham correction equation instead of the most commonly used Bazett equation. Indeed, the Bazett equation is known to be most sensitive to biasing effects of HR which appear to be particular important in the context of weight loss since weight loss is often accompanied by a reduction in HR. It should be noted, however, that the extent of

Table 1 Overview on previous studies on the effects of weight loss on the length of the corrected QTc interval

Study	Included subjects	Intervention	Follow-up period	Achieved weight loss	Used correction formula	Changes in QTc interval	Changes in heart rate (HR)	Comment
Alpert et al. [5]	n = 39 (31 female) without heart failure (HF) n = 28 (23 female) with HF	Bariatric surgery	Nadir of postoperative weight loss (5.0 ± 0.6 months)	Estimated ΔBMI was −10.9 kg/m^2 Estimated ΔBMI was −13.0 kg/m^2	Bazett Bazett	Estimated ΔQTc was −34.1 ms Estimated ΔQTc was −18.2 ms	Estimated ΔHR was −0.8 bpm Estimated ΔHR was −0.8 bpm	Weight loss reduced significantly QTc in severely obese humans with and without HF.
Al-Salameh et al. [6]	n = 28, 25 female	Sleeve gastrectomy	3 months after intervention	Mean weight loss was 21 ± 8 kg	Bazett	Bazett −28 ± 16 ms	Not mentioned	Sleeve gastrectomy significantly reduced QTc in severely obese humans.
Pontiroli et al. [7]	n = 24, 13 female	Gastric banding vs. hypocaloric diet	6 month after gastric banding	ΔBMI was −7.5 ± 3.6 kg/m^2	Not mentioned	QTc correlated positively with diastolic blood pressure	Estimated ΔHR was −8 bpm	Weight reduction induced by bariatric surgery associated with recovery of a more physiological autonomic control of cardiovascular function
Mukerji et al. [8]	n = 39, 31 female	Bariatric surgery	Nadir of weight loss	ΔBMI was −10 ± 2.7 kg/m^2	Bazett	Bazett −18.2 ± 10.6 ms	ΔHR was −0.8 ± 2.0 bpm	Prospective cohort study where weight loss induced changes of QTc and left ventricular mass were investigated.
Gondoni et al. [9]	n = 270, 108 female	Hypocaloric diet + physical activity	23 ± 4 days	BMI decreased by 3.1 %	Bazett Fridericia Framingham	Bazett −3 ms (significant decrease) Fridericia +2 ms (significant increase) Framingham +2 ms (non-significant)	HR decreased by −8.3 %	Physical training and diet did not relevantly influence QTc in obese subjects.
Alam et al. [10]	n = 11, 8 female	Gastric banding (n = 6) and biliopancreatic diversion (n = 5)	1, 6, 12 months	BMI decreased by 24 % at 1-year follow-up (both procedures combined)	Bazett Fridericia	QTc (Bazett and Fridericia) did not significantly alter in response to weight loss 12 months after bariatric intervention	HR decreased significantly (−8.6 bpm) in response to weight loss 12 months after bariatric intervention	Cardiac changes in response to bariatric surgery depend rather on weight loss.
Russo et al. [11]	n = 100, 58 female	Bilio-intestinal bypass	12 months	Estimated ΔBMI was −10.4 kg/m^2	Bazett	Estimated ΔQTc was −44.6 ms 12 months after bypass surgery	Estimated ΔHR was −10.7 bpm 12 months after bypass surgery	Weight loss causes reduction of parameters proposed to ventricular repolarization.
Bezante et al. [12]	n = 55, 42 female	Biliopancreatic diversion	12 months	-61 ± 13 % weight loss	Bazett	Estimated ΔQTc was −26 ms 12 months after bariatric intervention	QTc was significantly correlated with HR	Biliopancreatic diversion reduces QT interval in severely obese patients.
Seyfeli et al. [21]	n = 30, 24 female	Conventional weight loss program	12 weeks	Mean weight loss was −14.5 ± 5.0 kg	Bazett	Estimated ΔQTc was −7 ms	HR did not change	QTc tended to be significantly reduced in response to weight loss but not heart rate.
Pontiroli et al. [13]	n = 41, female 33, hypertensives n = 75, female 63, normotensives	Gastric banding	12 months	Estimated ΔBMI was −8.3 and −8.0 kg/m^2, respectively	Bazett	Estimated ΔQTc was −15.4 ms and −16.5 ms, respectively	Not mentioned	Weight loss significantly reduces QTc.
Papaioannou et al. [14]	n = 17, 11 female	Vertical band gastroplasty	8–10 months	Excess weight loss of 48.7 ± 6.7 %	Bazett	Estimated ΔQTc was −35 ms	Estimated ΔHR was −8 bpm	Weight loss significantly shortened QTc values.
Gupta et al. [15]	n = 63, 60 female	Liquid protein diet for 26 weeks	26 weeks	Group I (n = 57): Estimated mean	Bazett			In a subgroup of patients (n = 57), QTc decreased

Table 1 (continued)

Study	Included subjects	Intervention	Follow-up period	Achieved weight loss	Used correction formula	Changes in QTc interval	Changes in heart rate (HR)	Comment
				weight loss was −25 kg Group II (n = 6): Estimated mean weight loss was −28 kg		Group I (n = 57): Estimated mean ΔQTc was −8 ms Group II (n = 6) Estimated mean ΔQTc was −15 ms	Group I (n = 57): Estimated mean ΔHR was −7 bpm Group I (n = 6): Estimated mean ΔHR was −12 bpm	significantly after weight loss.
Mshui et al. [16]	n = 36, 18 female	Behavioural therapy combined with very low-calorie diet	5 year	8 % mean weight loss	Bazett	Estimated ΔQTc was −11 ms	Estimated ΔHR was 4 bpm	Weight reduction significantly shortened QTc values in obese humans.
Pietrobelli et al. [17]	n = 30, 15 female	Balanced formula diet	7 days	−3.9 ± 1.7 kg	Bazett	Estimated ΔQTc was −7 ms, P = 0.11	No measurable effect on RR interval was observed	An amelioration of prolonged baseline QTc has been observed.
Carella et al. [18]	n = 522, 411 female	Very low-calorie diet	26 weeks	Mean weight loss was −23 kg	Bazett	Estimated ΔQTc was −10 ms (manually accessed) Estimated ΔQTc was −10 ms (automated accessed)	Not mentioned	The study authors concluded that QT interval shortens with weight loss.
Doherty et al. [19]	n = 12 (all female) n = 8 (all female)	Very low-calorie diet Balanced-deficit diet	3, 9, 13, 17, 19 and 45 weeks	−22.4 kg after 45 weeks −14.5 kg after 45 weeks	Bazett	Estimated ΔQTc was −20 ms Estimated ΔQTc was −10 ms	HR reduced by −10.9 % HR reduced by −9.7 %	No significant reductions of QTc values in response to weight loss
Rasmussen et al. [20]	n = 22 (all female)	Gastroplasty surgery	6 months	Mean weight loss was −28.4 kg	Bazett	Estimated ΔQTc was −1 ms	Not mentioned	Weight loss due to gastroplasty surgery did not impact on QTc.
Corbi et al. [22]	n = 66 obese women, 30 WHR >0.85 (group A), 36 WHR ≤ 0.85 (group B), n = 25 nonobese control women	Multidisciplinary approach (diet, exercise, behavioural and nutritional counselling	6, 12 months	Estimated ΔBMI was −5.0 and 4.6 kg/m^2, respectively	Bazett	Decrease of QTc interval and QTc dispersion was greater in group A than group B (P < 0.01 and P < 0.02, respectively).	Not mentioned	Decline in weight loss was correlated with decline in QTc.

weight loss induced by a hypocaloric diet and exercise in the abovementioned negative study [9] was only moderate, i.e. a BMI reduction of −1.2 kg m^{-2}. Thus, the finding of unchanged QTc interval length after weight loss in this study may not pertain to greater amounts of weight loss as typically achieved by bariatric surgery. Support for this assumption may generate from a recent meta-analysis of 11 studies that investigated QT intervals after weight loss [23]. Here, it was found that the reduction of QTc interval length was more pronounced in the six studies in which the weight loss was achieved by bariatric surgery than in the five studies that used non-surgical measures.

An intriguing previous finding in the context of QTc interval investigation after bariatric surgery was that a shortening was already observed 4 weeks after biliopancreatic diversion (BPD) surgery in one study [12]. Moreover, despite a marked progressive weight loss, a further shorting of QTc was not observed thereafter [12]. This finding suggests that QTc interval shorting might not only represent a consequence of weight loss [6, 12] but could also result from dramatic metabolic changes as a consequence of bariatric surgery. Insulin may play a particular role in this context, since bariatric surgery has been shown to rapidly reduce circulating insulin levels [24]. Moreover, several previous cross-sectional studies have revealed an independent association between circulating insulin levels and QTc interval length [25, 26]. Interventional studies, however, have revealed a less consistent picture where intravenous insulin infusion acutely increased QTc interval length in normal weight [27] but not in obese subjects [28] under euglycemic conditions.

Therefore, we addressed two questions in the present study: Firstly, does, and if so to what extent, shorting the QTc interval length after bariatric surgery depends on the used HR correction equation, and, secondly, are changes in QTc interval length related to concurrent changes in circulating insulin levels or other metabolic traits?

Methods

Selection of Patients and Study Design

For the purpose of our study, we extracted data from a large, prospectively maintained database including data from severely obese subjects who have undergone bariatric surgery. Inclusion criteria for the study were the existence of an ECG recording within 3 months before and 1 year after bariatric surgery. Exclusion criteria were the intake of any drugs known to affect QTc interval length [29], a known heart disease and any kind of arrhythmia or bundle blocks in the ECG recordings. We identified 49 severely obese patients who fulfilled these criteria. Concurrent clinical data including anthropometric measures, blood pressure and metabolic blood parameters were also extracted from the database. Nine (18 %) of 49 obese patients had type 2 diabetes with 5 of them taking oral anti-diabetic drugs alone and 4 of them in combination with insulin.

Surgical Procedure

All procedures were carried out by the same surgeon (Martin Thurnheer). Seven subjects underwent a standard proximal Roux-en Y gastric bypass (RYGB) procedure and 42 subjects a distal RYGB variant as previously described [30].

Clinical Assessments

All subjects underwent a standardized clinical assessment before and 1 year after RYGB surgery. This included a venous blood sampling in the morning (8:00–10:00 h) after overnight fasting, the measurement of body weight, waist circumference, brachial blood pressure by use of appropriate, arm circumference adjusted cuffs (*OSZ 5 Easy*, Welch Allyn, Jungingen, Germany), an bioelectrical impedance analysis for determination of body composition (*Nutriguard-M*, Data-Input GmbH, Darmstadt, Germany) and a 12-lead ECG recording (*Schiller* CS-200, Schiller Medizintechnik GmbH, Germany), which was measured in a supine position after a rest of at least 10 min. Glucose, insulin, triglycerides, low-density and high-density lipoproteins and high sensitive C-reactive protein (hsCRP) concentrations were measured in serum samples.

ECG Analyses

Electronically recorded ECGs were analysed in accordance to current recommendations [31]. HR was calculated upon respective RR intervals. QTc was measured from the earliest onset of the Q-wave to the latest end of the T-wave. In the presence of a U-wave, the T-wave end was defined by the nadir between the two of them. At least three consecutive beats were analysed and respective QT intervals were averaged for further analysis. To avoid inter-observer bias, all analyses of ECG recordings were performed by one examiner (Erik Konrad Grasser).

Correction of QT intervals for HR (RR interval) was performed by using the following four established equations: Bazett's equation ($QTc = QT/RR^{0.5}$) [32], Fridericia's equation ($QTc = QT/RR^{0.33}$) [33], Framingham's equation ($QTc = QT + 0.154\,(1000 - RR)$) [34] and Hodges's equation ($QTc = QT + 1.75\,(\text{heart rate} - 60)$) [35].

QT dispersion (QTD) was assessed as the difference between the maximum QT interval (QT_{max}) and the minimum QT interval (QT_{min}) length across the 12 leads. Corrected QT dispersion (QTcD) was calculated by correcting QT_{max} and QT_{min} by using the four different equations, i.e. Bazett, Fridericia, Framingham

and Hodges ($QTcD_{Bazett}$, $QTcD_{Fridericia}$, $QTcD_{Framingham}$ and $QTcD_{Hodges}$), before subtracting respective QTc_{min} from QTc_{max} values.

Calculations and Statistical Data Analysis

The following indices were calculated upon the assessed data: homeostasis model assessment (HOMA), i.e. an estimate of insulin resistance (HOMA-IR), was calculated by using the following formula: HOMA-IR = [fasting insulin ($\mu IU\ mL^{-1}$) x fasting glucose ($mmol\ L^{-1}$)] / 22.5 [36]. Excessive weight loss (EWL %) was calculated as (preoperative weight minus current weight) / (preoperative weight minus height [cm] + 100) × 100. Total weight loss [kg] was calculated as current weight minus preoperative weight and relative weight loss [%] as (current weight minus preoperative weight) / (preoperative weight) × 100.

All data are reported as means ± standard deviation (SD). Variables were tested for normality using the D'Agostino Pearson omnibus normality test. Pairwise comparisons were performed using a paired Student's *t* test. Repeated measures ANOVA with the Newman-Keuls post hoc testing was used to compare between the four corrected QT intervals and dispersions. Prevalence of patients with QTc prolongation >440 ms before vs. after RYGB surgery was compared by McNemar test. Pearson correlation analysis was used to assess associations between QTc changes in QTc intervals (i.e. ΔQTc = QTc after RYGB − QTc before RYGB) and other concurrently assessed variables. Multivariate regression analyses were performed to detect independent associations. All reported *P* values are two sided. For all tests, significance was set at $P < 0.05$.

Results

Data on anthropometric, cardiovascular and metabolic variables before and 1 year after the RYGB surgery are provided in Table 2. The average weight loss across the 1-year postoperative period was 48.9 ± 14.8 kg which translates to a relative weight loss of 37.2 ± 6.5 %, a BMI loss of 17.3 ± 4.4 kg m^{-2} and a EWL of 72.4 ± 18.6 % (all $P < 0.001$). Body fat mass (FM), percentage FM and waist circumference were also significantly reduced after the surgery (all *P*s < 0.001). Importantly, HR decreased on average by 19.1 ± 10.4 bpm, as did SBP and DBP (all *P*s < 0.001).

Metabolic blood variables were markedly improved after the surgery as glucose, insulin, HOMA-IR, hsCRP, triglycerides, total cholesterol and low-density lipoprotein levels were significantly lower and high-density lipoprotein levels significantly higher after than before the surgery (all *P*s < 0.05).

QTc Interval Length Before and After RYGB Surgery

QTc values calculated upon the different correction equations before and after the RYGB surgery are provided in Table 3. Before the RYGB surgery, QTc intervals calculated upon the Bazett's equation were significantly longer than calculated upon the three other equations ($P < 0.001$ for all comparisons).

One year after the RYGB surgery, QTc_{Bazett} interval length was on average −30.6 ± 18.2 ms shorter than before the surgery ($P < 0.001$). The extent of QTc shortening was much smaller when the other three correction equations were used ($QTc_{Fridericia}$ −11.5 ± 14.7 ms, $Qtc_{Framingham}$ −13.5 ± 14.8 ms, QTc_{Hodges} - 9.0 ± 14.6 ms; all *P*s < 0.001 for comparison with $\Delta QTc_{Bazett,}$; Fig. 1) but still significant (all *P*s < 0.001 for comparison with corresponding preoperative values).

The number of patients showing a QTc_{Bazett} interval length of greater than 440 ms significantly decreased from 14 preoperatively to 2 postoperatively ($P < 0.001$), whilst with the other correction equations, only 3 to 1 patients showed a QTc interval length >440 ms before the surgery and none of the patients after the surgery.

Correlation and Multivariate Regression Analyses Before RYGB Surgery

Preoperative QTc_{Bazett} did not correlate with any other of the assessed variables ($P > 0.05$), whilst $QTc_{Fridericia}$ inversely correlated with body weight ($r = -0.40$; $P = 0.004$), hip circumference ($r = -0.32$; $P = 0.03$) and waist circumference ($r = -0.35$; $P = 0.02$). $QTc_{Framingham}$ inversely correlated with HR ($r = -0.29$; $P = 0.04$), weight ($r = -0.42$; $P = 0.003$), hip circumference ($r = -0.34$; $P = 0.02$) and waist circumference ($r = -0.36$; $P = 0.01$). QTc_{Hodges} was inversely correlated with weight ($r = -0.34$; $P = 0.02$).

Multivariate regression analysis indicated no significant association of any of the assessed variable with QTc_{Bazett} before the surgery. In contrast, respective analysis on the other three QTc variables, i.e. $QTc_{Fridericia}$, $QTc_{Framingham}$ and QTc_{Hodges}, showed a very consistent picture with preoperative values being significantly related to HR and insulin (Table 4).

Correlation and Multivariate Regression Analyses After RYGB Surgery

In response to RYGB surgery, changes in QTc interval length (ΔQTc) correlated with changes in HR (ΔHR) when using the Bazett's equation ($P < 0.001$), which could not be found when using Fridericia's ($P = 0.73$), Framingham's ($P = 0.91$) or Hodges's equation ($P = 0.88$) (Fig. 2). Interestingly, irrespectively of the used correction equation, changes in the QTc interval length (ΔQTc) did not correlate with preoperative QTc values (all *P*s > 0.09; Fig. 3).

Table 2 Anthropometric, blood and cardiovascular data of subjects before (*pre*) and 12 months after (*post*) Roux-en-Y gastric bypass (RYGB)

Variable	Pre Mean ± SD	Post Mean ± SD	*P* value	*n*
Age, years	38.7 ± 11.0	40.1 ± 11.0	<0.001	49
Height, m	1.67 ± 0.10	1.67 ± 0.10	1.0	49
Weight, kg	130.0 ± 25.1	81.1 ± 15.2	<0.001	49
Body mass index, kg m^{-2}	46.2 ± 6.7	29.0 ± 4.5	<0.001	49
Waist, cm	131 ± 17	94 ± 11	<0.001	46
Hip, cm	140 ± 15	106 ± 10	<0.001	46
Fat mass, kg	61.2 ± 15.2	23.1 ± 9.5	<0.001	43
Fat mass, %	47.3 ± 6.4	28.1 ± 8.8	<0.001	43
Total Cholesterol, mmol L^{-1}	4.9 ± 1.1	3.3 ± 0.7	<0.001	45
Low density lipoprotein, mmol L^{-1}	2.8 ± 0.8	1.4 ± 0.5	<0.001	43
High density lipoprotein, mmol L^{-1}	1.3 ± 0.3	1.4 ± 0.3	0.03	45
Triglycerides, mmol L^{-1}	1.9 ± 1.1	1.1 ± 0.5	<0.001	45
High sensitive C-reactive protein, μU mL^{-1}	9.7 ± 6.8	1.4 ± 1.9	<0.001	44
Glucose, mmol L^{-1}	6.1 ± 2.3	4.8 ± 0.9	0.001	30
Insulin, mU L^{-1}	18.6 ± 11.5	4.8 ± 4.6	<0.001	38
HOMA-IR	5.5 ± 4.7	1.3 ± 1.7	<0.001	30
Heart rate, bpm	79.6 ± 10.0	60.6 ± 9.0	<0.001	49
Systolic blood pressure, mmHg	132.7 ± 14.6	117.7 ± 13.0	<0.001	41
Diastolic blood pressure, mmHg	87.7 ± 10.4	74.1 ± 12.9	<0.001	41

Statistical analysis was performed using a paired students *t* test, and $P < 0.05$ was considered as significant difference

n number of patients, *SD* standard deviation, *HOMA-IR* homeostasis model assessment of insulin resistance

Postoperative changes in the QTc_{Bazett} interval length (ΔQTc_{Bazett}) were significantly correlated with changes in BMI ($r = 0.32$; $P = 0.03$), absolute weight loss ($r = 0.31$; $P < 0.05$), HR ($r = 0.60$; $P < 0.001$) and hsCRP levels ($r = 0.38$; $P < 0.05$). Postoperative changes in QTc_{Hodges} were significantly correlated with changes in total cholesterol ($r = 0.37$; $P < 0.05$) and LDL ($r = 0.33$; $P < 0.05$) levels. No bivariate correlations were found between the assessed variables and changes in $QTc_{Fridericia}$ and $QTc_{Framingham}$ values.

Multivariate regression analysis revealed that changes in QTc_{Bazett} were independently associated with changes in HR ($R^2 = 0.29$; $B = 0.69$; SEM = 0.26; $P < 0.05$) and changes in QTc_{Hodges} were independently associated with changes in total

Table 3 Calculations of average QT and corrected QT intervals (QTc) and presentation of patients with QTc ≥ 440 ms before (*pre*) and after (*post*) gastric bypass surgery using four different equations to calculate QTc ($n = 49$, 35 females)

	QT	QTc_{Bazett}	$QTc_{Fridericia}$	$QTc_{Framingham}$	QTc_{Hodges}
Pre, ms	374 ± 26	429 ± 21	410 ± 20[b]	410 ± 18[b]	409 ± 19[b]
Post, ms	399 ± 24	398 ± 23	398 ± 19	397 ± 20	400 ± 19
P value[a]	<0.001	<0.001	<0.001	<0.001	<0.001
Patients ≥440 ms	–	QTc_{Bazett}	$QTc_{Fridericia}$	$QTc_{Framingham}$	QTc_{Hodges}
Pre, *n* (%)	–	14 (29 %)	3 (6 %)	3 (6 %)	1 (2 %)
Post, *n* (%)	–	2 (4 %)	0 (0 %)	0 (0 %)	0 (0 %)
P value	–	< 0.001	–	–	–

All data are expressed as the mean ± SD, and statistical significance was set at $P < 0.05$. No changes were found comparing the postsurgery QTc intervals

QTc_{Bazett} QTc evaluation using Bazett's formula ($QTc = QT/RR^{0.5}$), $QTc_{Fridericia}$ QTc evaluation using Friderica's formula ($QTc = QT/RR^{0.33}$), $QTc_{Framingham}$ QTc evaluation using Framingham's formula ($QTc = QT + 0.154(1000 - RR)$), QTc_{Hodges} QTc evaluation using Hodges's formula ($QTc = QT + 1.75$ (heart rate − 60))

[a] Comparisons between *pre* and *post* conditions were performed using a paired *t* test

[b] $P < 0.005$, statistical significant difference compared with pre-QTc_{Bazett} using repeated measures ANOVA with Newman-Keuls post hoc testing

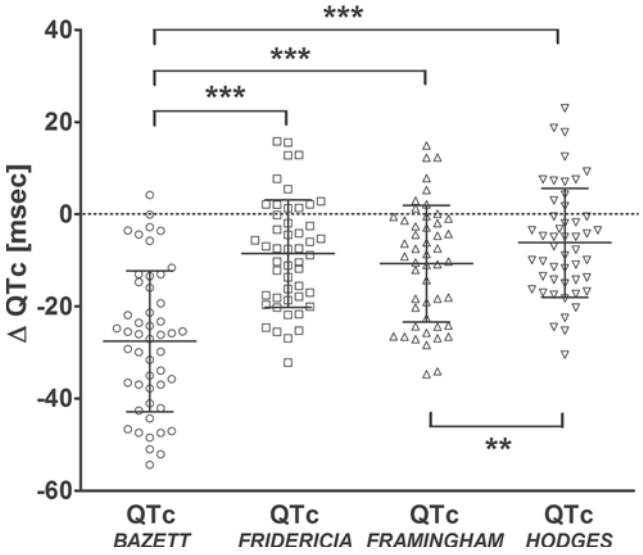

Fig. 1 QTc changes in 49 subjects (35 females) (i.e. QTc after RYGB subtracted by QTc before RYGB = ΔQTc) depicted as scatter dot plot (means ± SD) using four different QT correction equations (i.e. QTc_{Bazett}, $QTc_{Fridericia}$, $QTc_{Framingham}$ and QTc_{Hodges}). Repeated measures ANOVA with Newman-Keuls post hoc testing was used to compare changes in QTc between the four equations and statistical significance was set at $P < 0.05$. $^{**}P < 0.01$, statistical significant difference between QTc_{Hodges} and $QTc_{Framingham}$ and $^{***}P < 0.005$, statistical significant difference between QTc_{Bazett} and $QTc_{Fridericia}$, $QTc_{Framingham}$ and QTc_{Hodges}

cholesterol ($R^2 = 0.3$; $B = 16.5$; SEM = 4.1; $P = 0.001$) and LDL ($R^2 = 0.21$; $B = -14.8$; SEM = 5.7; $P < 0.05$).

QT Dispersion

QTD values did not significantly change after the RYGB surgery (before 40.0 ± 14.4 vs. after 41.7 ± 14.5 ms; $P = 0.58$). This was also true after correcting QTD for HR by using the correction equations (before vs. after; $QTcD_{Bazett}$ 45.2 ± 16.3 vs. 41.1 ± 14.0 ms; $P = 0.19$; $QTcD_{Fridericia}$ 43.3 ± 15.6 vs. 41.0 ± 14.1 ms; $P = 0.47$; $QTcD_{Framingham}$ 40.0 ± 14.4 vs. 41.7 ± 14.5 ms; $P = 0.58$; $QTcD_{Hodges}$ 40.0 ± 14.4 vs. 41.7 ± 14.4ms; $P = 0.58$). Of note, there were differences between QTcD calculated upon the four different equations neither before nor after the RYGB surgery (all Ps > 0.25).

Discussion

To our best knowledge, we are the first to show a consistent reduction of QTc interval length by using four different QT correction equations in response to excessive weight loss after undergoing a RYGB surgery procedure. However, the extent of QTc interval shortening clearly depends on the applied correction equation with an overestimation when using Bazett's equation, which also appears to be most sensitive to changes in HR. Furthermore, whilst QTc interval length appears to be cross-sectionally associated with serum insulin levels, postoperative changes in the hormone concentrations as well as in other assessed metabolic variables were not found to be consistently associated with QTc interval shorting recorded 1 year after RYGB surgery. Taken together, our findings clearly support the previous notion of a QTc interval shorting associated with weight loss, the underlying mechanisms of which require further investigations.

An abnormal QTc prolongation represents an independent risk factor for sudden cardiac death [3, 31]. In our study, 29 % of the severely obese patients showed a QTc interval length above 440 ms when the Bazett formula was used for HR correction. Moreover, the percentage of patients showing a QTc interval length above this cutoff was markedly reduced to 4 % after the RYGB surgery. In light of this finding, it is tempting to conclude that an improvement of ventricular repolarization could represent a relevant factor for the reduction of mortality upon bariatric surgery that has previously been documented in large-scale observational studies [37, 38]. However, this notion is clearly challenged by our observation of substantial reduced patients showing prolonged QTc intervals when a correction equation other than Bazett's has been used. Moreover, the lack of any correlation between the preoperative QTc interval length and respective changes after the surgery renders it rather unlikely that the shorting of QTc intervals represents a normalization of a pathological condition associated with the weight loss. Of note, to date it is not even clear whether the obesity-associated QT interval prolongation and its reduction after weight loss is overall related to the incidence of cardiac arrhythmia that can result in sudden cardiac deaths. Further studies exploiting technologies for

Table 4 Multivariate regression model with $QTc_{Fridericia}$, $QTc_{Framingham}$ and QTc_{Hodges} as dependent variable prior to RYGB surgery (n = 49, 35 females)

	Heart rate				Insulin			
	R^2	B	SEM	P value	R^2	B	SEM	P value
$QTc_{Fridericia}$	0.33	−1.53	0.37	0.001	0.19	0.84	0.34	<0.05
$QTc_{Framingham}$	0.36	−1.48	0.34	0.001	0.19	0.80	0.31	<0.05
QTc_{Hodges}	0.26	−1.28	0.38	<0.01	0.17	0.75	0.34	<0.05

HR heart rate, *SEM* standard error of the means

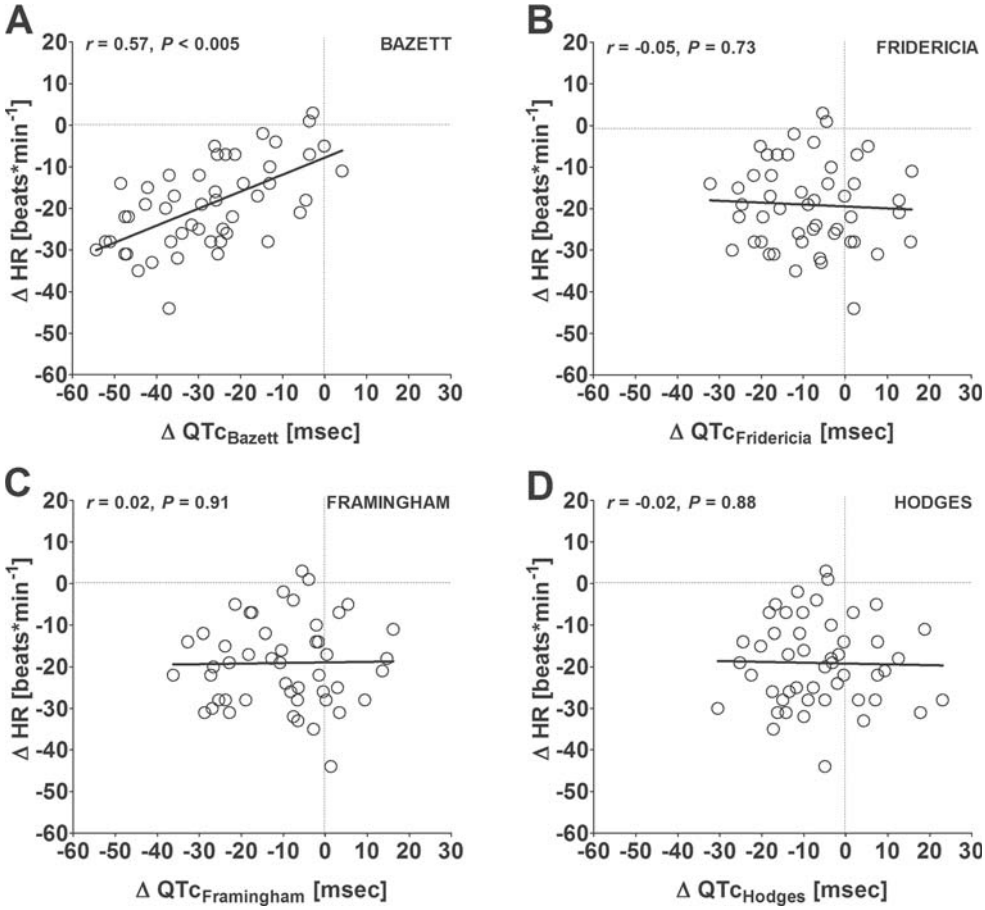

Fig. 2 Linear regression analysis in 49 subjects (35 females) including statistics (Pearson correlation coefficient *r* and the corresponding *P* value) for the relation between mean changes in QTc_{Bazett} (**a**), $QTc_{Fridericia}$ (**b**), $QTc_{Framingham}$ (**c**) and QTc_{Hodges} (**d**) to mean changes in heart rate (HR) (i.e. HR after RYGB subtracted by HR before RYGB = ΔHR). $P < 0.05$ was considered as statistical significant

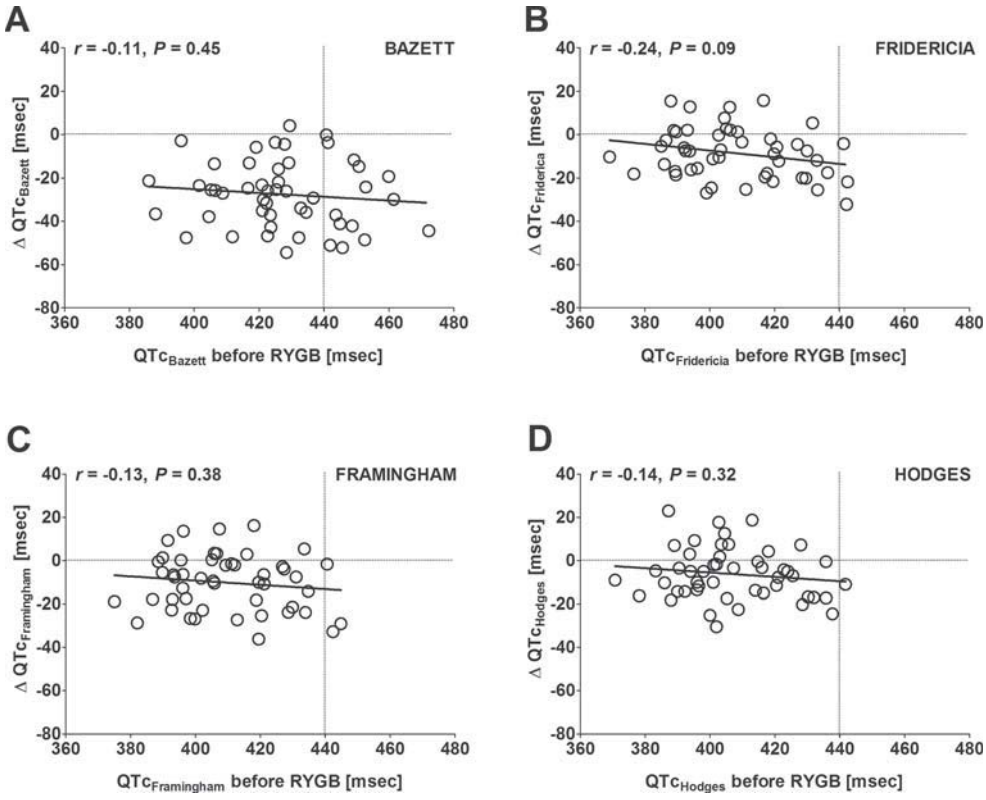

Fig. 3 Linear regression analysis in 49 subjects (35 females) including statistics (Pearson correlation coefficient *r* and the corresponding *P* value) for the relation between QTc_{Bazett} (**a**), $QTc_{Fridericia}$ (**b**), $QTc_{Framingham}$ (**c**) and QTc_{Hodges} (**d**) before RYGB to their respective mean changes (i.e. QTc after RYGB subtracted by QTc before RYGB = ΔQTc). $P < 0.05$ was considered as statistical significant

continuous cardiac monitoring such as implantable loop recorders are needed to answer this important question in the future.

The mechanisms underlying QTc interval shortening as a consequence of weight loss remain largely unknown. In our study, we were unable to find a consistent association of any of the assessed metabolic variables with postoperative changes in QTc interval length. In particular, we did not find a correlation between the postoperative decline in circulating insulin levels and the QTc interval shortening. Insulin appeared to be a most likely mediator of the weight loss associated QT interval reduction [39] since the hormone is well known to increase sympathetic nervous system (SNS) activity [40] and circulating catecholamine levels [41] that strongly affect myocardial repolarization. In light of our data, however, it appears rather unlikely that the reduction of circulating insulin levels represent a major factor in this context. Since RYGB surgery is known to induce such a wide range of metabolic changes [42], it appears still likely that specific metabolic or endocrine signals that we have not captured in our study contribute to the observed QTc interval shortening. For instance, free fatty acids (FFAs) may represent a good candidate since one previous study [22] has found a correlation between the decline in circulating FFA levels and the QTc interval length reduction after diet-induced weight loss. Also, the adipose tissue hormone leptin may be a good candidate since it was shown to decline after bariatric surgery along with a marked reduction in SNS activity [43]. Beside these putative hormonal mediators, other mechanisms may also contribute to the weight loss associated reduction in QT interval length. For instance, it is well documented that obesity leads to enhanced cardiac fat deposits, which might also impact on ventricular repolarization, but are likely decline with weight loss. Also, a reduction in subclinical ventricular hypertrophy or sleep apnoea/hypopnoea after bariatric surgery that has not been captured in our current study could have an important impact on myocardial repolarization. Putting this forward, further research is clearly in need to pinpoint the underlying mechanisms of weight loss associated QT interval length reduction.

QT dispersion did not change after RYGB surgery in our study, i.e. a finding that is in contrast to previous findings. A recent meta-analyses of seven studies [23] investigating QT dispersion after weight loss found a reduction of QT dispersion in six of the studies. Of note, QT dispersion was corrected for HR by using the Bazett's equation in five of these studies and HR changes associated with weight loss were reported only in four of these studies, with two of them showing a clear reduction in HR. Overall, there is no evidence that QT dispersion depends on HR and it has elegantly been shown that a QT dispersion correction for HR by using the Bazett's equation can produce invalid results in particular when there is a difference in HR [44]. On the background of our negative finding and the outlined methodological considerations, we believe that it remains unclear whether or not weight loss affects QT dispersion.

Several limitations of our study should be mentioned. First, the limited number of patients and the overrepresentation of women did not allow us to test for putative sex differences. Second, since our study includes patients with diabetes, albeit to a very limited percentage, i.e. 18 %, we cannot exclude that established autonomic neuropathy have biased QT interval results in some of the patients. Lastly, we were unable to obtain data on SNS activity, sleep-related disordered breathing and other variables that could contribute to the reduction of QTc interval length after the surgically induced weight loss.

Conclusion

The findings of our study clearly support the previous notion of QTc interval shortening in response to weight loss. However, our finding that the extent of QTc interval changes in response to a bariatric surgery induced weight loss largely depends on the applied HR correction equation calls the clinical significance of obesity and weight loss associated QTc interval alterations into question. Thus, our results may stimulate other researchers to also apply other than Bazett's correction equation in future studies and probably also on already existing database, in order to elucidate the important question as to whether the weight loss associated QT interval shortening reduces the risk of cardiac arrhythmia and sudden death in obesity.

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Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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